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(54) Method of female contraception and kit for use in such method

(57) The present invention is concerned with a method of contraception in a female mammal of childbearing capability, said method comprising orally administering to the female a combination of estrogen and progestogen continuously for at least 3 months, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof, said estrogen being administered in an amount equivalent to a daily oral dosage of 2.2-5 mg 17β-estradiol and said progestogen being administered in an amount equivalent to a daily oral dose of 5-50 mg dydrogesterone.

Another aspect of the invention relates to a kit comprising a plurality of oral dosage units, said plurality of daily hormone units containing an estrogen in an amount equivalent to 2.2-5 mg 17β-estradiol and a progestogen in an amount equivalent to 5-50 mg dydrogesterone, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof.

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Description

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention is concerned with a new method of contraception in mammalian females of childbearing capability. More particularly the present invention relates to such a method comprising orally administering to the female a combination of estrogen and progestogen continuously for at least 3 months.

[0002] The invention also relates to a pharmaceutical kit comprising a plurality of oral dosage units, said plurality of daily hormone units containing an estrogen and a progestogen.

BACKGROUND OF THE INVENTION

[0003] Currently on the market there are a number of hormonal contraceptives for females which can be classified into two general types. The first are known as monophasic preparations. These contain a constant amount of an estrogen and a progestogen. Newer preparations known as bi- or triphasic preparations have varying levels of estrogen and progestogen; in most cases consisting of relatively constant levels of estrogen with a step-wise increase in progestogen throughout the cycle. This pattern of estrogen and progestogen administration results in a relatively dominant estrogenic formulation at the beginning of the package with increasing progestogenic activity toward the end of the package. Mono-, bi- and triphasic contraceptives are commonly referred to as combined contraceptives.

[0004] Virtually all combined contraceptives have in common that they are based on a regimen which involves an administration-free interval of about 7 days whereby withdrawal bleeding, simulating the natural menses, occurs. Thus 21 day intervals of hormone administration alternate with 7 days during which no hormones are administered.

[0005] As an alternative to the aforementioned combined contraceptive methods, the so called sequential method has been proposed. Typical of the sequential contraceptive method is that it comprises two consecutive phases, i.e. one phase during which estrogen and no progestogen is administered and another phase during which a combination of estrogen and progestogen is administered. The first sequential methods, like the aforementioned combined contraceptives, made use of an administration free interval of about 7 days. More recently, sequential methods have been proposed which do not include such an administration-free (or placebo) period, meaning that estrogen is administered throughout the full cycle and that progestogen is co-administered during only part of that cycle. WO 95/17895 (Ehrlich et al.) describes such an uninterrupted sequential method.

[0006] Yet another alternative contraceptive method that employs continuous uninterrupted administration of progestogen and at least one estrogen is described in WO 99/12531. In contrast to the aforementioned combined and sequential contraceptive methods, no regular menses occur as the continuous administration of progestogen in the indicated amounts induces amenorrhoea. This so called continuous combined method offers the advantage that it prevents withdrawal bleedings. In addition, the method gives rise to less subjective complaints, such as the symptoms caused by hormone fluctuations, and is associated with a lower risk of VTE than the well-known combined and sequential regimens. Finally, it is believed that the avoidance of chronic fluctuations in blood serum steroid levels may have a positive impact on the occurrence of premenstrual syndrome and the risk of breast cancer.

SUMMARY OF THE INVENTION

[0007] As mentioned above, a continuous combined contraceptive method that employs a combination of an estrogen and a progestogen is known from WO 99/12531. The present inventors have unexpectedly discovered that significantly less unscheduled bleeding and spotting is observed in such a continuous combined method if the estrogen 17β-estradiol (E2) is employed and is administered in a dosage that is significantly higher than that advocated in the PCT-application.

[0008] In addition, it was surprisingly found that the prolonged use of a combination of a relatively high dose of E2 and a progestogen very effectively suppresses endometrial thickening. This finding indicates that a continuous combined method employing a relatively high dose of E2 may be used advantageously as a contraceptive method.

[0009] It is very unexpected that, despite the use of a high dose of E2, the present method does not give rise to significant endometrial thickening since E2, like other estrogens, is usually associated with endometrial stimulation.

DETAILED DESCRIPTION OF THE INVENTION

[0010] Accordingly, one aspect of the invention is concerned with a method of contraception in a female mammal of childbearing capability, said method comprising orally administering to the female a combination of estrogen and progestogen continuously for at least 3 months, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof, said estrogen being administered in an amount equivalent to a daily oral dosage of 2.2-5 mg 17β-estradiol and said progestogen being administered in an amount equivalent to a daily oral dose of 5-50 mg dydrogesterone.

[0011] The combination of estrogen and progestogen is advantageously administered at least once daily so as to maintain a relatively constant serum concentration. Most preferably the combination is administered

once daily.

[0012] The present method may suitable employ any pharmaceutically acceptable substance with sufficient progestogenic activity. The present invention encompasses the use of substances that exhibit progestogenic activity per se as well as precursors of such substances. The invention also encompasses the use of progestogen metabolites that exhibit progestogenic activity. Examples of progestogens that may suitably be employed in accordance with the invention include dydrogesterone, norethisterone, levonorgestrel, norgestimate, drospirenone, 3-beta-hydroxydesogestrel, 3-keto desogestrel, 17-deacetyl norgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrodydrogesterone, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogestone acetate, gastrinon, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol, medrogestone, medroxyprogesterone, megestrol, melengestrol, nomegestrol, norethindrone (=norethisterone), norethynodrel, norgestrel, norgestrienone, normethisterone, progesterone, quingestanol, (17alpha)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, trimegestone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime, precursors of these progestogens and combinations thereof. Preferably, the progestogen is selected from the group consisting of dydrogesterone, dihydrodydrogesterone, norethisterone, levonorgestrel, desogestrel, norgestimate, drospirenone, cyproterone, gestodene, trimegestone, progesterone, precursors of these progestogens and combinations thereof. Even more preferably, the progestogen is selected from the group consisting of dydrogesteron, dihydrodydrogesterone, norethisterone, precursors of these progestogens and combinations thereof. Most preferably, the progestogen is dydrogesterone, dihydrodydrogesterone or a precursor thereof.

[0013] The present method may suitably employ a precursor of 17β-estradiol or a precursor of the progestogen. Such precursors are capable of liberating 17β-estradiol or a progestogen when used in the present method, e.g. as a result of metabolic conversion. Examples of suitable precursors of 17β-estradiol and progestogens include such substances wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; tetrahydrofuranyl; tetrahydropyranal; or a straight or branched chain glycosidic residue containing 1-20 glycosidic units per residue.

[0014] Typical examples of precursors which can suitably be used in accordance with the invention are esters that can be obtained by reacting the hydroxyl groups of the estrogenic substances with substances that contain one or more carboxy (M^+ ^-OOC-) groups, wherein M^+ represents a hydrogen or (akali)metal cation. Hence, in a particularly preferred embodiment, the precursors are derivatives of 17β-estradiol or a progestogen, wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by -CO-R, wherein R is a hydrocarbon radical comprising from 1-25 carbon atoms. Preferably R is hydrogen, or an alkyl, alkenyl or aryl radical comprising from 1-20 carbon atoms.

[0015] An important advantage of the present method resides in the fact that it suppresses endometrial growth. Typically, in the present method, the continuous administration of the combination of estrogen and progestogen is effective in maintaining a substantially constant thin endometrium with a thickness of less than 8 mm, preferably of less than 6 mm.

[0016] The continuous administration of the combination of estrogen and progestogen is advantageously continued for a period of at least 4 months, more preferably for a period of at least 6 months. Most preferably, the present method employs continuous combined administration of the two steroids for at least 9 months.

[0017] The term "continuous" as used in here, means that the combination of estrogen and progestogen is administered at relatively regular intervals, with no (therapeutically) significant interruptions. Naturally, minor interruptions may occur that do not affect the overall effectiveness of the present method, and indeed such aberrations are encompassed by the present invention. In a preferred embodiment, and more arithmetically, the administration regimen is deemed to be continuous if the longest interval between 2 subsequent administrations is not more than 3.5 times as long as the average interval. Even more preferably said longest interval is not more than 2.5 times, most preferably not more than 1.5 times as long as the average interval.

[0018] The present method requires continuous administration of the combination of estrogen and progestogen for a period of at least 3 months. In order to minimise the risk of so called breakthrough bleeding, it can be advantageous to periodically interrupt the continuous administration for a period of 4-12 days, preferably for a period of 5-9 days. These interruptions will cause a predictable withdrawal bleeding, following which continuous administration of the combination of estrogen and progestogen can be resumed with a reduced risk of breakthrough bleeding. Preferably, such an interruption occurs after 3-12 months of continuous administration, more preferably after 3-8 months and most preferably after 3-6 months of continuous administration. In a particularly preferred embodiment, the present method employs a protocol with at least 2 interruptions following periods of continuous combined administration.

[0019] As explained before, it is a critical element of the present invention to administer a relatively high dose

of estrogen. In a particularly preferred embodiment the estrogen is administered in an amount equivalent to a daily oral dosage of at least 2.4 mg 17β-estradiol, more preferably of at least 2.5 mg and most preferably of at least 2.6 mg 17β-estradiol. Preferably, the estrogen is administered in a dosage that does not exceed an amount equivalent to a daily oral dosage of 4.5 mg 17β-estradiol, more preferably it does not exceed an amount equivalent to a daily oral dosage of 4 mg 17β-estradiol and most preferably, it does not exceed an amount equivalent to a daily oral dosage of 3.5 mg 17β-estradiol.

[0020] In another preferred embodiment of the present method the progestogen is administered in an amount equivalent to a daily oral dosage of 8-30 mg dydrogesterone, more preferably in an amount equivalent to a daily oral dosage of 10-20 mg dydrogesterone. The equivalent daily oral dosages for the progestogen norethisterone acetate may be calculated by dividing the recommended dosages for dydrogesterone by 10. Similarly, equivalent dosages for other progestogens may be obtained by using conversion factors that are known in the art or that may be established by methods well known to the person skilled in the art.

[0021] The amount of estrogen administered in accordance with the present method is preferably effective to achieve a 17β-estradiol serum concentration of at least 30 pg/ml, more preferably of at least 50 pg/ml.

[0022] The present method is particularly suitable for treating humans, primates, bovines, porcines, equines, canines or felines. Most advantageously the present method is employed in the treatment of humans.

[0023] It was found that the present method is particularly advantageous in non-smoking females. Although the inventors do not wish to be bound by theory it is believed that smoking interferes with E2-metabolisation in a way that reduces the bioavailability of E2, e.g. by increasing 2-hydroxylation of E2. Thus, the present method is preferably employed to prevent conception in a non-smoking human female.

[0024] It was surprisingly found that the anti-proliferative effect of the present combination of estrogen and progestogen on the endometrium may be enhanced further by co-administration of an androgen. In addition, the continuous co-administration of an androgen in the present contraceptive regimen offers the advantage of even less vaginal breakthrough spotting and bleeding. Consequently, in another preferred embodiment of the invention, the present method comprises co-administration of an androgen.

[0025] Preferably, in the present method, androgen is co-administered in an amount effective to maintain the serum androgen concentration of the female mammal at a level equivalent to between 0.5 and 5.0, preferably between 0.7 and 4.0 and most preferably between 1.0 and 3.0 nanomoles testosterone per litre. Here the testosterone concentrations relate to the total testosterone present in the serum, i.e. including both free testosterone and bound testosterone.

[0026] The androgen used in the present method is preferably selected from the group consisting of dehydroepiandrosterone (DHEA); DHEA-sulphate; testosterone; testosterone esters such as testosterone undecanoate , testosterone propionate, testosterone phenylpropionate, testosterone isohexanoate, testosterone enantate, testosterone bucanate, testosterone decanoate, testosterone buciclate; danazol; gestrinone; methyltestosterone; mesterolon; stanozolol; androstenedione; dihydrotestosterone; androstanediol; metenolon; fluoxymesterone; oxymesterone; methandrostenolol; 7α-methyl-19-nortestosterone (MENT); precursors capable of liberating these androgens when used in the present method and mixtures thereof. Most preferably the androgen is selected from the group consisting of DHEA, danazol, gestrinone, testosterone esters, androstenedione, precursors capable of liberating these androgens when used in the present method and mixtures thereof. Preferably the testosterone esters employed in the present method comprise an acyl group which comprises at least 6, more preferably from 8-20 and preferably 9-13 carbon atoms. Most preferably the androgens used in the present method are DHEA and/or testosterone undecanoate. These androgens offer the advantage that they can effectively be used in oral dosage units.

[0027] It is noted that, for instance, DHEA, testosterone undecanoate and androstenedione are precursors of testosterone and that said precursors *per se* exhibit virtually no affinity for androgen receptors in the female body. The effectiveness of the androgens within the method of the invention is determined by their functionally active form, which may well be different from the form in which they are administered.

[0028] In a preferred embodiment the androgen is provided in an amount equivalent to a daily oral dosage of 5 to 250 mg DHEA, which is equivalent to a daily oral dosage of 1 to 50 mg testosterone undecanoate. More preferably the androgen is provided in an amount which is equivalent to a daily oral dosage of 10-120 mg DHEA. Most preferably the androgen is administered in an amount which is equivalent to a daily oral dosage of 20-60 mg DHEA.

[0029] Another aspect of the invention relates to a kit comprising a plurality of oral dosage units, said plurality of daily hormone units containing an estrogen in an amount equivalent to 2.2-5 mg 17β-estradiol and a progestogen in an amount equivalent to 5-50 mg dydrogesterone, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof. Because the present kit is intended for use in a continuous combined contraceptive method, said kit preferably does not contain dosage units that do not contain a combination of estrogen and progestogen. Even more preferably, the kit does not contain any dosage units that do not contain the combination of estrogen and the progestogen in the indicated amounts.

[0030] Typically, the present kit contains at least 40 dosage units, preferably at least 60, more preferably at least 100 dosage units. These dosage units may be held in a container, or alternatively they may be held in a strip from which they may be removed individually by the user.

[0031] The invention is further illustrated by means of the following examples.

EXAMPLES

Example 1

[0032] A clinical study was conducted in 30 young healthy female volunteers (15 smokers and 15 non-smokers) who were using a combined monophasic oral contraceptive with at least 30 microgram ethinyl estradiol at the moment of enrolment.

[0033] Immediately following 19-25 days of taking this monophasic oral contraceptive, without observing a tablet-free period, treatment with the study medication was commenced. The study medication comprised of continuously administering 3 mg 17beta-estradiol (E2) combined with 1.5 mg norethisterone acetate without pauses for 3 months. Follicular development and endometrial thickness were measured by ultrasonography once every 3 or 4 days depending on follicle growth. Vaginal spotting and bleeding was scored daily by the participants in a diary. In addition, endocrine measurements (E2 and progesterone) were performed in a subgroup of the participants (4 individuals who exhibited follicular growth, 5 randomly selected non-smokers and 5 randomly selected smokers). Specific contraceptive side-effects, mood changes and volunteer appreciation were also evaluated.

[0034] No ovulations were observed in any of the participants. In 4 of the 30 participants (2 smokers and 2 non-smokers) persistent follicles of 25-30 mm were seen. In these women, no increase in the progesterone levels was observed. No dominant follicles were seen in the other 26 women (median diameter 5 mm). Endometrial thickness did not change during treatment (median 4.5 mm before and 4.0 mm after treatment). After an initial adaptation period spotting was found to occur infrequently in 3 out of 15 non-smokers. In smokers however bleeding and spotting occurred in 3 out of 15 women and spotting only in another 5 women. In some women breast tension, bloating and acne occurred during treatment. No mood changes were registered. Of the 30 participating women, 12 would use this contraceptive when available and 12 would consider its use.

Example 2

[0035] Example 1 is repeated with the exception that the participants continuously receive 3 mg 17beta-estradiol (E2) combined with 15 mg dydrogesterone without pauses for 4 months. Similar results are obtained as described in Example 1.

Example 3

[0036] The study described in Example 2 is repeated with the exception that after the period of 4 months of continuous combined administration, the participants receive placebo's during 7 subsequent days, resulting in withdrawal bleeding in all subjects. Immediately following these 7 days, the participants again receive the combination of E2 and dydrogesterone uninterruptedly for another 4 months. Following this period of 4 months the women yet again receive placebo's during 7 subsequent days. Also this time, withdrawal bleeding is observed in all participants during the placebo period.

[0037] In parallel, another group of 30 women, which women were selected on the basis of the same criteria mentioned in Example 1, receives the combination of E2 and dydrogesterone continuously, i.e. without interruptions, during a period of 8 months and 14 days.

[0038] It was found that the incidence of bleeding and spotting in the latter group was significantly higher than in the group that alternately received the combination of E2 and dydrogesterone for 4 months followed by an administration-free interval of 7 days.

Claims

1. Use of an estrogen in the manufacture of a pharmaceutical preparation for use in a method of contraception in a female mammal of childbearing capability, said method comprising orally administering to the female a combination of estrogen and progestogen continuously for at least 3 months, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof, said estrogen being administered in an amount equivalent to a daily oral dosage of 2.2-5 mg 17β-estradiol and said progestogen being administered in an amount equivalent to a daily oral dose of 5-50 mg dydrogesterone.

2. Use according to claim 1, wherein the progestogen is selected from the group consisting of dydrogesterone, norethisterone, levonorgestrel, norgestimate, drospirenone, 3-beta-hydroxydesogestrel, 3-keto desogestrel, 17-deacetyl norgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrodydrogesterone, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogestone acetate, gastrinon, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol, medrogestone, medroxyprogesterone, megestrol, melengestrol, nomegestrol, norethin-

drone (=norethisterone), norethynodrel, norgestrel, norgestrienone, normethisterone, progesterone, quingestanol, (17alpha)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, trimegestone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime, precursors of these progestogens and combinations thereof.

3. Use according to claim 2, wherein the progestogen is selected from the group consisting of dydrogesterone, dihydrodydrogesterone, norethisterone, levonorgestrel, desogestrel, norgestimate, drospirenone, cyproterone, gestodene, trimegestone, progesterone, precursors of these progestogens and combinations thereof.

4. Use according to claim 3, wherein the progestogen is dydrogesterone, dihydrodydrogesterone or a precursor thereof.

5. Use according to any one of the preceding claims, wherein the precursor of 17β-estradiol is an ester of 17β-estradiol.

6. Use according to any one of claims 2-4, wherein the precursor of the progestogen is an ester of said progestogen.

7. Use according to any one of the preceding claims, wherein the continuous administration of the combination of estrogen and progestogen is effective in maintaining a substantially constant endometrial thickness of less than 8 mm, preferably of less than 6 mm.

8. Use according to any one of the preceding claims, wherein the estrogen is administered in an amount equivalent to a daily oral dosage of 2.4-4 mg 17β-estradiol, preferably to a daily oral dosage of 2.5-3.5 mg 17β-estradiol.

9. Use according to any one of the preceding claims, wherein the progestogen is administered in an amount equivalent to a daily oral dosage of 8-30 mg dydrogesterone, preferably to a daily oral dosage of 10-20 mg dydrogesterone.

10. Use according to any one of the preceding claims, wherein the estrogen is administered in an amount effective to achieve a 17β-estradiol serum concentration of at least 30 pg/ml.

11. A kit comprising a plurality of oral dosage units, said plurality of daily hormone units containing an estrogen in an amount equivalent to 2.2-5 mg 17β-estradiol and a progestogen in an amount equivalent to 5-50 mg dydrogesterone, wherein the estrogen is selected from the group consisting of 17β-estradiol, precursors of 17β-estradiol and combinations thereof.

12. A kit according to claim 11, wherein the kit does not contain dosage units that do not contain the estrogen and the progestogen in the indicated amounts.

13. A kit according to claim 11 or 12, wherein the kit contains at least 40 dosage units, preferably at least 100 dosage units.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 03 07 5905

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	7 August 2003	Veronese, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 03 07 5905

Reason for the limitation of the search:

In view of the term "precursor" and of the definition of the amounts of the estrogen and of the progestogen given in claim 1 and 11, these and the corresponding dependent claims relate to an extremely large number of possible compounds and compositions. In fact, the claims contain so many options that a lack of clarity (and conciseness) within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely for compositions comprising 17-B-estradiol and esters thereof in combination with a progestogen, and their use in a contraceptive method.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 03 07 5905

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
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X	US 4 383 993 A (HUSSAIN ANWAR A ET AL) 17 May 1983 (1983-05-17) * examples 1,2 *	11-13	
E	WO 03 041719 A (COELINGH-BENNINK HERMAN JAN TI ;PANTARHEI BIOSCIENCE B V (NL); VAN) 22 May 2003 (2003-05-22) * claims 6,7,15,16 * * page 11, line 30 - page 12, line 18 *	11-13	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 03 07 5905

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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07-08-2003

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